Chapter 5
Etiology and Epidemiology of Cholera

Isolates of *Vibrio cholerae* serogroup O1 are classified into two biotypes, El Tor and classical, on the basis of several phenotypic characteristics. Currently, the El Tor biotype is responsible for virtually all of the cholera cases throughout the world, and classical isolates are not encountered outside of Bangladesh. In addition *V. cholerae* O1 is classified into two serotypes, Inaba and Ogawa, based on agglutination in antiserum. A possible third serotype, Hikojima, has been described, but it is very rare. During an outbreak or epidemic, it is worth documenting the biotype and serotype of the isolate; however, it is not necessary to know this information to respond appropriately to the epidemic.

Within the O1 and O139 serogroups, the ability to produce cholera toxin (CT) is a major determinant of virulence. In general, isolates of *V. cholerae* O1 or O139 that produce CT are considered fully virulent and capable of causing epidemic cholera (Table 5-1). Most *V. cholerae* isolated during cholera outbreaks will be toxigenic serogroup O1 or O139. However, some isolates of *V. cholerae* O1 do not produce CT and cannot cause epidemic cholera. When these isolates are encountered, they must be considered within their clinical and epidemiologic context. Nontoxigenic isolates may be associated with sporadic diarrheal disease.

A. Historical Background

Cholera is thought to have its ancestral home in the Ganges Delta of the Indian subcontinent. In the nineteenth century, pandemic waves of cholera spread to many parts of the world. In 1961, a massive epidemic began in Southeast Asia; this is now recognized as the beginning of the seventh cholera pandemic. This pandemic was caused by the El Tor biotype of toxigenic *V. cholerae* O1. It spread rapidly through south Asia, the Middle East, and southeastern Europe, reaching Africa by 1970. In January 1991, epidemic cholera appeared in South America in several coastal cities of Peru and spread rapidly to adjoining countries. By the end of 1996, cholera had spread to 21 countries in Latin America, causing over 1 million cases and nearly 12,000 deaths. The number of cholera cases reported elsewhere in the world has also increased in the 1990s. In Africa in the early 1990s, the primary focus of cholera was in southern Africa. However, in the latter part of the decade, the focus moved to west Africa. Overall, more cases were reported from Africa in the 1990s than in a similar time period in previous decades.

Vibrio cholerae serogroup O139

Vibrio cholerae serogroup O139 appeared in India in late 1992. It quickly spread to Bangladesh and other Asian countries, although the rate of spread has slowed after the initial outbreaks. Through 1998, 11 countries have officially

reported transmission of *V. cholerae* O139 to WHO. Imported cases have been reported from the United States and other countries. At this time, *V. cholerae* O139 appears to be confined to Asia.

Table 5-1. Comparison of epidemic- and non-epidemic-associated *V. cholerae* strains

Typing systems	Epidemic-associated	Non-epidemic-associated
Serogroups	O1, O139	Non-O1 (>150 exist)
Biotypes for serogroup O1	Classical and El Tor (not applicable to serogroup O139)	Biotypes are not applicable to non-O1 strains
Serotypes for serogroup O1	Inaba, Ogawa, and Hikojima (not applicable to serogroup O139)	These 3 serotypes are not applicable to non-O1 strains
Toxin production	Produce cholera toxin[a]	Usually do not produce cholera toxin; sometimes produce other toxins

[a] Nontoxigenic O1 strains exist but are rarely associated with epidemics.

The epidemiologic characteristics of the O139 serogroup are similar to those of the O1 serogroup. The isolation and identification characteristics of the O139 serogroup are identical to those of the O1 serogroup except that O139 antiserum is needed for identification. Biotyping tests for *V. cholerae* O1 are not valid for *V. cholerae* O139 or any non-O1/O139 serogroup.

B. Clinical Manifestations

Cholera is a secretory diarrheal disease. The enterotoxin produced by *V. cholerae* O1 and O139 causes a massive outpouring of fluid and electrolytes into the bowel. This rapidly leads to profuse watery diarrhea, loss of circulation and blood volume, metabolic acidosis, potassium depletion, and ultimately vascular collapse and death. In severe cases, purging diarrhea can rapidly cause the loss of 10% or more of the body's weight, with attendant hypovolemic shock and death; however, 75% or more of initial infections with *V. cholerae* O1 or O139 may be asymptomatic, depending on the infecting dose. Of the 25% of persons with symptomatic infections, most have mild illness. Approximately 5% of patients have moderate illness that requires medical attention but not hospitalization. In only about 2% of patients does the illness progress to life-threatening "cholera gravis." Persons with blood type O are more likely to develop severe cholera than those with other blood types.

C. Treatment

Successful treatment of cholera patients depends on rapid replacement of fluid and electrolyte losses. With proper treatment, mortality is less than 1% of reported cases. Fluids and electrolytes can be replaced rapidly through either oral or intravenous routes. Intravenous therapy is required for patients who are in profound shock or cannot drink.

Antimicrobial therapy is helpful, although not essential, in treating cholera patients. Antimicrobial agents reduce the duration of illness, the volume of stool, and the duration of shedding of vibrios in the feces. When antimicrobial agents are used, it is essential to choose one to which the organism is susceptible. Antimicrobial agents recommended by WHO for treating cholera patients include tetracycline, doxycycline, furazolidone, trimethoprim-sulfamethoxazole, erythromycin, or chloramphenicol. Ciprofloxacin and norfloxacin are also effective. Because antimicrobial resistance has been a growing problem in many parts of the world, the susceptibility of *V. cholerae* O1 strains to antimicrobial agents should be determined at the beginning of an epidemic and be monitored periodically (see Annexes C and E).

For *V. cholerae*, the results of disk diffusion tests for ampicillin, sulfonamides, tetracycline, and trimethoprim-sulfamethoxazole (i.e., percentage of susceptible, intermediate, and resistant) correlate well with the minimum inhibitory concentration (MIC) results determined by broth microdilution. Disk diffusion tests should not be used for doxycycline and erythromycin because the results for these drugs are frequently inaccurate for *V. cholerae* O1 and O139 strains. However, the tetracycline disk test can be used to predict the likely susceptibility of isolates to doxycycline. Additional details on antimicrobial susceptibility testing are given in Chapter 9.

D. Epidemiology

When cholera first appears in epidemic form in an unexposed population, it can affect all age groups. In contrast, in areas with high rates of endemic disease, most of the adult population have gained some degree of natural immunity because of illness or repeated asymptomatic infections. In this setting, the disease occurs primarily in young children, who are exposed to the organism for the first time, and in the elderly, who have lower gastric acid production and waning immunity. The poor are at greatest risk because they often lack safe water supplies, are unable to maintain proper hygiene within the home, and may depend on street vendors or other unregulated sources for food and drink.

Numerous investigations have linked cholera transmission to drinking water drawn from shallow wells, rivers or streams, and even to bottled water and ice. Food is the other important means of cholera transmission. Seafood has repeatedly been a source of cholera, particularly raw or undercooked shellfish harvested from sewage-contaminated beds or from environments where *V. cholerae* O1 occurs naturally. Although *V. cholerae* O1 and O139 are easily killed by drying, sunlight, and acidity, they grow well on a variety of moist

alkaline foods from which other competing organisms have been eliminated by previous cooking. Cooked rice is an excellent growth medium, as are lentils, millet, and other cooked grains and legumes with neutral pH. Fruits and vegetables grown in sewage and eaten without cooking or other decontaminating procedures are potential vehicles of cholera transmission. Freezing foods or drinks does not prevent cholera transmission.

Person-to-person spread through direct contact, as by shaking hands or touching or by taking care of a patient, has not been shown to occur. Outbreaks on crowded hospital wards are likely to be due to contaminated food or water. Likewise, outbreaks following the funeral of a cholera patient have been caused by eating contaminated foods served at the wake, often prepared by the same persons who prepared the body for burial.

E. Cholera Vaccine

During the past 15 years, considerable progress has been made in the development of new oral vaccines against cholera. Two oral cholera vaccines, which have been evaluated with volunteers from industrialized countries and in regions with endemic cholera, are commercially available in several countries: a killed whole-cell *V. cholerae* O1 in combination with purified recombinant B subunit of cholera toxin (WC/rBS); and an attenuated live oral cholera vaccine, containing the genetically manipulated *V. cholerae* O1 strain CVD 103-HgR. The appearance of *V. cholerae* O139 has redirected efforts to develop an effective and practical cholera vaccine. None of the currently available vaccines is effective against this strain.

References

Global Task Force on Cholera Control. Guidelines for cholera control. Geneva: World Health Organization; 1992. Publication no. WHO/CDD/SER/80.4 Rev 4.

Centers for Disease Control and Prevention. Laboratory methods for the diagnosis of *Vibrio cholerae.* Atlanta, Georgia: CDC, 1994.